REMARKS

The new claims differ from the previous claims by not containing the product-by-process language. Thus, the new claims are linguistically pure product claims. This change in claims imposes no burden whatsoever on the PTO because the scope of examination for product-by-process claims, of course, is the same for product claims lacking the process language since the latter is ignored in PTO examination. Thus, there is no question regarding constructive elections or any burden whatsoever on the PTO. The scopes of examination and searches are precisely the same.

The prior art rejections, it is respectfully submitted, must be withdrawn. Both hinge on EP 344134 which represents earlier work of one of the inventors of this application, Dr. Zardi. The EP document appears to disclose an antibody BC-1; (e.g., page 6, line 44 and its four figures) which binds to a protein sequence coded by the exon ED-B of human fibronectin (FN). However, this turns out not to be true.

The specification of this application make this clear. See pages 4 and 5, in particular, lines 26-29 of page 5, expressly stating that BC-1 does not bind directly to ED-B. Rather, it seems that BC-1 requires the presence of the ED-B domain in the FN in order for it to bind to FN. This turns out not to be due to direct binding of BC-1 to the ED-B domain. Rather, it binds instead to an adjacent portion of FN. See also Carnemolla (reference BA, as initialed by the examiner on Form PTO 1449). In this reference, note in particular the second sentence of the abstract which expressly states this fact. Regarding the differences between BC-1 and this invention also see the specification at page 31, lines 25-29, page 33, lines10-14, page 35, lines 4-9, etc.

As can be seen, the fundamental underpinning of the examiner's rejection turns out to be incorrect based on facts stated in the specification of this application and facts stated in peer reviewed journals. In this regard, see also Carnemolla et al. (Reference BB of record). Thus, both prior art rejections must be withdrawn.

As explained from page 5, line 34 though page 6, line 15, for example, of the specification, the prior art deficit was overcome by using synthetic phage libraries instead of standard hybridoma technology as the means for generating a specific binding member, e.g., an antibody, binding to the ED-B domain. Once the disclosure of this application was made public, it became routine for skilled workers to generate any number of ED-B specific binding members using any of the methods well

known, such as antibodies based on molecular libraries. That this is a highly conventional technology is clear, e.g., from the references cited in the specification at the top of page 6. Given the disclosure of this application, any of the many available techniques based on synthetic libraries can be employed to provide binding members within the scope of the claims. In view of the particular facility of libraries aimed at generating antibodies and antibody fragments, etc., claim 57 is especially clearly enabled, although all claims are enabled for the reasons discussed herein.

With respect to the examiner's comments on the searching of a large number of compounds, such screening is highly routine as of the filing date of this application and its priority application. As to the routineness of screening and the nondeterminative nature (with respect to enablement) of the time required to achieve such screening, see In re Wands, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1989). Finally, with respect to the comments made by the examiner in paragraph 12 of the office action, it is not understood why any guidance as to a particular conformation itself is necessary for enablement. The routine methods for generating specific binding members such as antibodies and antibody fragments etc. rely on inherent capabilities of the methods to screen for successful matches. Precise knowledge of involved conformations is not needed.

It is presumed that the rejection of paragraph 13 would now be applied to method claim 51 which corresponds to previous claim 27. This rejection is also untenable.

Firstly, the Federal Circuit has consistently and emphatically made clear that the PTO cannot make a utility rejection, whether explicitly under 35 USC 101, or as here, under the guise of an enablement rejection, unless it provides reasons or evidence to doubt the truth of the statements made in the specification which attest to the fact that the claimed invention works as stated and can routinely be used as stated. On this basis alone, the rejection is untenable. No such reasons or evidence has been provided. A mere allegation that the field of treating tumors is unpredictable is per se insufficient. See, e.g., In re Brana, 51 F. 3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995). As stated in Brana, even the FDA accepts applications for approval of drugs irrespective of whether the involved disease is easily or even never before treated.

For this particular application, evidence of the reasonableness of applicant's disclosure is strong, although unnecessary. For example, as noted in the paragraph bridging pages 14 and 15, the specific binding members of this invention specifically bind to tumors expressing or associated with

ED-B. Thus, they can be used as diagnostic agents, which the examiner does not contest. Because of this specific binding, they can also be used as therapeutic agents based, e.g., on a variety of techniques employed in the prior art for other types of antibodies specific to proteins on cell surfaces. See, e.g., page 16, line 20 and the following paragraphs. As the examiner may be aware, there are a large number of antibody therapeutic agents based on the same principle which are approved or are awaiting approval by the FDA. Note the commercial product Herceptin™ used for treating breast cancer based on an antibody specific for the Her2 receptor on such tumors. Analogously here, the specific binding members of this invention can be employed to treat tumors, e.g., which express ED-B on their surfaces.

In addition to the generic disclosure in the specification mentioned above, the applicability of the claimed specific binding agents in therapy has been established in example 5 of the application which employs a standard animal model to demonstrate in vivo targeting of human tumors. See also example 6 which provides yet another model successfully demonstrating therapeutic efficacy.

The examiner attempts to place the burden on applicants to prove that tumors are obliterated or tumor growth is arrested. However, the burden is on the PTO to provide reasons or evidence, especially in the face of the specification, why it is doubted that therapeutic activity exists. In addition, case law states that only finitely detectable activity is needed for utility not obliteration or arrested tumor growth. The specification statement that the claimed agents are useful against tumors expressing the ED-B region is presumptively accurate and enabling. The rejection should be withdrawn.

The examiner's comments on the pharmaceutical composition claims are not understood. Pharmaceutical compositions are not necessarily limited to any particular therapeutic activity. They also encompass diagnostic uses. Just as a single use is sufficient to justify a broad scope of the compounds per se, a single use is also sufficient to justify a broad scope of pharmaceutical composition claims. Thus, this aspect of the rejection should be withdrawn also.

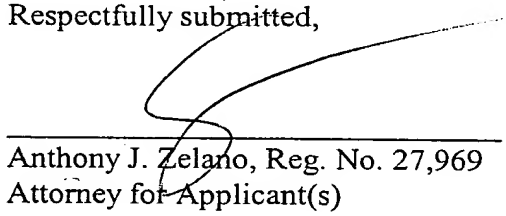
The examiner has rejected the previous employed phrase "synthetic molecular repertories." This phrase is no longer used. However, the previous phrase and the current new phrase "synthetic molecular library" are fully supported in the specification. See, for example, page 5, line 34 to the bottom of page 6. Page 6, line 1 refers to the use of conventional libraries and page 6, lines 30-31

refers to the fact that the claimed binding members can be naturally derived or wholly or partially synthetically produced. A skilled worker would clearly know that synthetic molecular repertories or libraries are disclosed. It is noted that the examiner had no difficulty recognizing that a synthetic molecular repertory was involved in EP 344134, demonstrating the routine nature of this term. Of course, as explained above and in the specification, '134 did not use such technology; rather, it used conventional hybridoma technology to produce its different antibody, BC-1.

The examiner is thanked for noting the various suggestions for improving the already clear nature of the claims. Most of these suggestions have been incorporated into the new claims where appropriate. "DP 47" has been eliminated from the claims because the requested SEQ IDs have been inserted which make this phraseology redundant. However, the specification fully explained the meaning of the phrase in any event. Lastly, the meaning of "effective" in the claims is clear to any skilled worker. For example, the amount at issue must serve the particular purpose involved within the scope of the claim at issue.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,



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Attorney Docket No. : NOTAR 3

Date: February 14, 2002

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE ABSTRACT:

The Abstract is added herein and therefore no marked-up version is necessary.

IN THE SPECIFICATION:

The paragraph on page 2, line 12-35 has been amended as follows:

Although there are obvious limitations to treating solid tumors through the targeting of tumor-associated antigens, these tumors do have a feature I common which provides an alternative antigenic target for antibody therapy. Once they have grown beyond a certain size, tumors are universally dependent upon an independent blood supply for adequate oxygen and nutrients to sustain growth. If this blood supply can be interfered with or occluded, there is realistic potential to starve thousands of tumor cells in the process. As a tumor develops, it undergoes a switch to an angiogenic phenotype, producing a diverse array of angiogenic factors which act upon neighboring capillary endothelial cells, inducing them to proliferate and migrate. The structure of these newly-formed blood vessels is highly disorganized, with blind endings and fenestrations leading to increased leakiness, in marked contrast to the ordered structure of capillaries in normal tissue. Induction of angiogenesis is accompanied by the ~~upregulatic of~~ upregulation of expression of certain cell surface antigens, many of ~~which e~~ which are common to the vasculature of normal tissues. ~~Identifyi ntigens~~ Identifying antigens which are unique to neovasculature of tumors has been the main limiting factor in developing a generic treatment of solid tumors through vascular targeting. The antigen which is the subject of the present invention addresses this problem directly.